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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jonathan A. Bard, et al.

Serial No.: Not Yet Known

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For: DNA ENCODING GALANIN GALR3 RECEPTORS AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
December 3, 2001

U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

Sir:

PRELIMINARY AMENDMENT AND IFORMATION DISCLOSURE STATEMENT

Applicants request that the following amendments be made to the above-identified application:

In the Specification:

Please delete the current Title on page 1, lines 4-5, and on page 236, line 1, and replace it with the following:

--**METHOD OF TREATING AN ABNORMALITY USING A GALR3 RECEPTOR ANTAGONIST**--

On page 1, after the title, please delete the current paragraph and insert the following new paragraph:

--This application is a continuation of U.S. Serial No. 09/058,333, filed April 9, 1998, now allowed, which is a continuation-in-part of PCT International Application No.

PCT/US97/18222, filed October 9, 1997, which is a continuation-in-part and claims priority of U.S. Serial No. 08/900,230, filed July 23, 1997, now allowed, which is a continuation-in-part of U.S. Serial No. 08/787,261, filed January 24, 1997, now abandoned, the contents of which are incorporated by reference. Throughout this application, various references are referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citation for these references may be found at the end of this application, preceding the sequence listing and the claims.--

Please delete the paragraph on page 8, line 33 through page 9, line 9 and insert the following replacement paragraph:

--This invention provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within one of the two strands of the nucleic acid encoding the GALR3 receptor contained in plasmid K1086. This invention still further provides a nucleic acid probe comprising 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence described in Figure 1 (SEQ ID NO: 1) or (b) the reverse compliment to the nucleic acid sequence shown in Figure 1 (SEQ ID NO: 1).--

Please delete the paragraph on page 9, lines 11-33, and insert

the following replacement paragraph:

--In yet another embodiment, the GALR3 receptor is the rat GALR3 receptor having substantially the same amino acid sequence as the amino acid sequence shown in Figure 2. In another embodiment, the GALR3 receptor is the rat GALR3 receptor having the amino acid sequence shown in Figure 2. In another embodiment, the GALR3 receptor is the human GALR3 receptor. In another embodiment, the GALR3 receptor is the human GALR3 receptor encoded by the coding sequence of plasmid pEXJ-hGalR3. This invention also provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within one of the two strands of the nucleic acid encoding the GALR3 receptor contained in plasmid pEXJ-hGalR3. This invention provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence described in Figure 3 (SEQ ID NO: 3) or (b) the reverse compliment to the nucleic acid sequence shown in Figure 3 (SEQ ID NO: 3).--

Please delete the paragraph on page 24, lines 3-6, and insert the following replacement paragraph:

--**Figure 1** Nucleotide coding sequence of the rat hypothalamic galanin GALR3 receptor (SEQ ID NO: 1), with partial 5' and 3' untranslated sequences. Start and stop codons are underlined.--

Please delete the paragraph on page 24, lines 7-10, and insert the following replacement paragraph:

--**Figure 2** Deduced amino acid sequence of the rat hypothalamic galanin GALR3 receptor (SEQ ID NO: 2) encoded by the rat nucleotide sequence shown in Figure 1.--

Please delete the paragraph on page 24, lines 12-15, and insert the following replacement paragraph:

--**Figure 3** Nucleotide coding sequence of the human galanin GALR3 receptor (SEQ ID NO: 3), with partial 5' and 3' untranslated sequences. Start and stop codons are underlined.--

Please delete the paragraph on page 24, lines 17-22, and insert the following replacement paragraph:

--**Figure 4** Deduced amino acid sequence of the human galanin GALR3 receptor (SEQ ID NO: 4) encoded by the human nucleotide sequence shown in Figure 3. The nucleotide sequence shown in Figure 3 is translated from nucleotide 1 to the stop codon. Two possible starting methionines are underlined.--

Please delete the paragraph on page 24, lines 24-29, and insert the following replacement paragraph:

--**Figures 5A-5D** Amino acid sequence alignment of the rat GALR3 receptor (top row) (SEQ ID NO: 2), human GALR3 receptor (middle row) (SEQ ID NO: 4) and rat GALR1 receptor (bottom row) (SEQ ID NO: 5). Transmembrane domains (TM 1-7) are indicated by brackets above the sequence.--

Please delete the paragraph on page 29, line 13 through page 30, line 3 and insert the following replacement paragraph:

--This invention provides an isolated nucleic acid encoding a GALR3 receptor having the same or substantially the same amino acid sequence as the amino acid sequence encoded by the plasmid K1086 (ATCC Accession No. 97747). In an embodiment, the nucleic acid is DNA. This invention further provides an isolated nucleic acid encoding a rat GALR3 receptor having the amino acid sequence encoded by the plasmid K1086. This invention provides an isolated nucleic acid encoding a GALR3 receptor having the same or substantially the same amino acid sequence as the amino acid sequence encoded by the plasmid pEXJ-RGalR3T (ATCC Accession No. 97826). In an embodiment, the nucleic acid is DNA. This invention further provides an isolated nucleic acid encoding a rat GALR3 receptor having the amino acid sequence encoded by the plasmid pEXJ-RGalR3T (ATCC Accession No. 97826). This invention provides an isolated nucleic acid encoding a GALR3 receptor having substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor is the rat GALR3 receptor having the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the nucleic acid comprises at least an intron. In still another embodiment, the nucleic acid comprises alternately spliced nucleic acid transcribed from the nucleic acid contained in plasmid K1086. In an embodiment, the alternately spliced nucleic acid is mRNA transcribed from DNA encoding a galanin receptor.--

Please delete the paragraph on page 30, lines 5-18 and insert the

following replacement paragraph:

--In an embodiment, the GALR3 receptor is a human GALR3 receptor. This invention provides an isolated nucleic acid encoding a human GALR3 receptor having the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). This invention provides an isolated nucleic acid encoding a human GALR3 receptor, wherein the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 34, line 33 through page 35, line 10 and insert the following replacement paragraph:

--This invention also provides an isolated galanin GALR3 receptor protein. In one embodiment, the GALR3 receptor protein has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor protein has the amino acid sequence encoded by plasmid K1086. In another embodiment, the protein has the amino acid sequence encoded by the plasmid pEXJ-hGalR3. In an embodiment, the GALR3 receptor protein has the same or substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In an embodiment, the GALR3 receptor comprises the same or substantially the same amino acid sequence as the amino acid sequence shown in Figure 4

(SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 38, lines 29-30, and insert the following replacement paragraph:

--This invention provides a plasmid designated M67 (ATCC Designation No. 209708).--

Please delete the paragraph on page 38, line 32 through page 39, line 1, and insert the following replacement paragraph:

--This plasmid (M67) was deposited on March 27, 1998, with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Designation No. 209708.--

Please delete the paragraph on page 40, line 35 through page 41, line 5 and insert the following replacement paragraph:

--This invention still further provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence shown in Figure 1 (SEQ ID NO: 1) or (b) the reverse complement to the nucleic acid sequence shown in Figure 1 (SEQ ID NO: 1).--

Please delete the paragraph on page 41, lines 7-20 and insert the following replacement paragraph:

--This invention also provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within one of the two strands of the nucleic acid encoding the GALR3 receptor contained in plasmid pEXJ-hGalR3. This invention provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence shown in Figure 3 (SEQ ID NO: 3) or (b) the reverse complement to the nucleic acid sequence shown in Figure 3 (SEQ ID NO: 3).--

Please delete the paragraph on page 48, line 16 through page 49, line 15 and insert the following replacement paragraph:

--In one embodiment, the GALR3 receptor is a mammalian GALR3 receptor. In another embodiment, the GALR3 receptor is a rat GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid K1086. In still another embodiment, the GALR3 receptor has the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In still another embodiment, the cells are transfected with the plasmid pEXJ-RGALR3T (ATCC Accession No. 97826), encoding the rat GALR3 receptor. Plasmid pEXJ-RGalR3T comprises the entire coding region of rat GALR3, but in

which the 5' initiating ATG is joined directly to the vector, and which comprises only 100 nucleotides from the 3' untranslated region after the stop codon (i.e., up to and including nucleotide 1275 in Figure 1 (SEQ ID NO: 1)). Transfection of cells with the "trimmed" plasmid results in a higher level of expression of the rat GALR3 receptor than the level of expression when plasmid K1086 is used. The use of the "trimmed" plasmid provides for greater convenience and accuracy in binding assays. In another embodiment the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In an embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 50, line 17 through page 51, line 4 and insert the following replacement paragraph:

--In one embodiment, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by the plasmid K1086. In yet another embodiment, the GALR3 receptor has the amino acid sequence encoded by the plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has

the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment of this invention the cells are transfected with plasmid pEXJ-RGalR3T (ATCC Accession No. 97826).--

Please delete the paragraph on page 51, line 29 through page 52, line 15 and insert the following replacement paragraph:

--In an embodiment, the GALR3 receptor is a mammalian GALR3 receptor. In one embodiment of the invention, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by the plasmid K1086. In still another embodiment, the GALR3 receptor has the amino acid sequence encoded by the plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or

substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 53, lines 17-19, and insert the following replacement paragraph:

--In an embodiment of any of the above processes, the cells are injected with RNA synthesized in vitro from the plasmid designated M67 (ATCC Designation No. 209708).--

Please delete the paragraph on page 58, line 34 through page 59, line 21 and insert the following replacement paragraph:

--In an embodiment of any of the above processes, the GALR3 receptor is a mammalian GALR3 receptor. In another embodiment of the above processes, the GALR3 receptor is a rat GALR3 receptor or a human GALR3 receptor. In still another embodiment of the above processes, the GALR3 receptor has the same or substantially the same amino acid sequence as encoded by the plasmid K1086 (ATCC Accession No. 97747). In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In still another embodiment, the GALR3 receptor has the same or

substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment of this invention the cells are transfected with plasmid pEXJ-RGalR3T (ATCC Accession No. 97826).--

Please delete the paragraph on page 61, line 20 through page 62, line 5 and insert the following replacement paragraph:

--In an embodiment of any of the above processes, the GALR3 receptor is a mammalian GALR3 receptor. In an embodiment of the above-described methods, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same

amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 63, lines 5-26, and insert the following replacement paragraph:

--In an embodiment of any of the above-described methods, the GALR3 receptor is a rat GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 64, line 33 through page 65, line 26, and insert the following replacement paragraph:

--In an embodiment of any of the above-described methods, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 (SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-RGalR3T (ATCC Accession No. 97826). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid M54 (ATCC Accession No. 209312). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid M67 (ATCC Designation No. 209708). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 68, line 32 through page 69,

line 15, and insert the following replacement paragraph:

--In an embodiment of any of the above-described processes, the GALR3 receptor is a mammalian GALR3 receptor. In another embodiment of any of the above-described processes, the GALR3 receptor has substantially the same amino acid as encoded by the plasmid K1086 (ATCC Accession No. 97747). In another embodiment of any of the above-described processes, the GALR3 receptor has substantially the same amino acid sequence as that shown in Figure 2 (SEQ ID NO: 2). In still another embodiment of any of the above-described processes, the GALR3 receptor has substantially the same amino acid sequence as encoded by the plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In an embodiment of any of the above-described processes, the GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as that shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427. In still another embodiment of any of the above-described processes, the GALR3 receptor has a sequence, which sequence comprises a sequence shown in Figure 4 (SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

Please delete the paragraph on page 98, lines 7-18, and insert the following replacement paragraph:

--Human brain multiple tissue northern blots (MTN brain blots II and III, Clontech, Palo Alto, CA) and human peripheral MTN blot (Clontech, Palo Alto, CA) carrying mRNA (2 µg) purified from various human brain areas and peripheral tissues, respectively, were hybridized at high stringency with overlapping probes directed to the amino-terminus of hGALR3

5' GATGGCTGATGCCCAGAACATTTCACTGGACAGCCCAGGGAGTGT 3'
(SEQ ID NO: 51) and
5' GACCACAGGCACTGCCACGGCCCCCACACTCCCTGGGCTGTCCAG 3'
(SEQ ID NO: 52), according to the manufacturer's specifications.--

Please delete the paragraph on page 98, lines 21-34, and insert the following replacement paragraph:

--Tissues were homogenized and total RNA extracted using the guanidine isothiocyanate/CsCl cushion method. RNA was then treated with DNase to remove any contaminating genomic DNA and poly A^+-selected using FastTrack kit (Invitrogen), according to manufacturer's specifications. cDNA was prepared from mRNA with random hexanucleotide primers using reverse transcriptase Superscript II (BRL, Gaithersburg, MD). First strand cDNA (corresponding to ≈5 ng of poly A^+ RNA) was amplified in a 50 µL PCR reaction mixture with 300 nM of forward (directed to the amino-terminus: (SEQ ID NO: 24) and reverse (directed to the third intracellular loop: (SEQ ID NO: 27) primers, using the thermal cycling program and conditions described above.--

Please delete the paragraph on page 98, line 37 through page 99, line 13, and insert the following replacement paragraph:

--The PCR products were run on a 1.5% agarose gel and transferred to charged nylon membranes (Zetaprobe GT, BioRad), and analyzed as Southern blots. GALR3 primers were screened for the absence of cross-reactivity with the other galanin receptors. Filters were hybridized with a radiolabeled probe directed to the first intracellular loop,

5'-TGCAGCCTGGCCCAAGTGCCTGGCAGGAGCCAAGCAGTACCACAG-3' (SEQ ID NO: 53), and washed under high stringency. Labeled PCR products were visualized on X-ray film. Similar PCR and Southern blot analyses were conducted with primers and probes directed to the housekeeping gene, glyceraldehyde phosphate dehydrogenase (G3PDH; Clontech, Palo Alto, CA), to normalize the amount of cDNA used from the different tissues.--

Please delete the paragraph on page 99, lines 15-27, and insert the following replacement paragraph:

--RT-PCR was performed on human pituitary cDNA (two sources: Clontech cDNA and cDNA prepared from poly A+RNA purchased from ABS) using the following conditions: 94°C for 30 sec and 68°C for 2 min, for 40 cycles, with a preincubation at 94°C for 2 min and a postincubation at 68°C for 5 minutes. Primers specific for human GALR1 were used (KS1177; SEQ ID NO: 35 and KS1178; SEQ ID NO: 36). Primers specific for human GALR2 were used (BB183; SEQ ID NO: 60 and BB184; SEQ ID NO: 61). Primers specific for human GALR3 were used (BB444; SEQ ID NO: 62 and BB445; SEQ ID NO: 63). Primers specific for human prolactin were used (BB446; SEQ ID NO: 64 and BB447; SEQ ID NO: 65).--

Please delete the paragraph on page 99, line 31 through page 100, line 8, and insert the following replacement paragraph:

--BB183: 5'-TCAGCGGCACCATGAACGTCTCGGGCT-3' (SEQ ID NO: 60).

BB184: 5'-GGCCACATCAACCGTCAGGATGCT-3' (SEQ ID NO: 61)

BB444: 5'-ATGGCTGATGCCCAGAACATTTCAC-3' (SEQ ID NO: 62).

BB445: 5'-TAGCGCACGGTGCCGTAGTAGCTGAGGT-3' (SEQ ID NO: 63).

BB446: 5'-ATGAAAGGGTCCCTCCTGCTGCTGCT-3' (SEQ ID NO: 64).

BB447: 5'-TATCAGCTCCATGCCCTCTAGAAGCC-3' (SEQ ID NO: 65).--

Please delete the paragraph on page 110, line 22 through page 112, line 10, and insert the following replacement paragraph:

--Oocytes were isolated as described above, except that 3 mg/mL collagenase was used to defolliculate the oocytes. Genes encoding G-protein inwardly rectifying K^+ channels 1 and 4 (GIRK1 and GIRK4) were obtained by PCR using the published sequences (Kubo et al., 1993; Dascal et al., 1993; Krapivinsky et al., 1995b) to derive appropriate 5' and 3' primers. Human heart cDNA was used as template together with the primers
5'-CGCGGATCCATTATGTCTGCACTCCGAAGGAAATTTG-3' (SEQ ID NO: 54) and
5'-CGCGAATTCTTATGTGAAGCGATCAGAGTTCATTTTTC -3' (SEQ ID NO: 55) for GIRK1 and
5'-GCGGGATCCGCTATGGCTGGTGATTCTAGGAATG-3' (SEQ ID NO: 56) and
5'- CCGGAATTCCCCTCACACCGAGCCCCTGG-3' (SEQ ID NO: 57) for GIRK4. In each primer pair, the upstream primer contained a BamHI site and the downstream primer contained an EcoRI site to facilitate cloning of the PCR product into pcDNA1-Amp (Invitrogen). The transcription template for hGalR3 was obtained similarly by PCR using the cloned cDNA in combination with primers
5'-CCAAGCTTCTAATACGACTCACTATAGGGCCACCATGGCTGATGCCCAGA-3' (SEQ ID NO: 58) and

5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGCAGGG TTTATTCCGGTCCTCG-3' (SEQ ID NO: 59). Alternatively, the complete coding region of hGalR3 is subcloned into the high-efficiency transcription vector pBS KS$^+$ AMV-pA50 (Nowak et al., 1995). This plasmid was modified by adding the recognition sequence for the restriction enzyme SrfI downstream of the poly A sequence in the plasmid. The new plasmid was designated M52. Subcloning involved the isolation of a 1.1 kb NcoI/EcoRI restriction fragment encoding the entire hGALR3 gene followed by its ligation into NcoI/EcoRI digested M52. After identification of a suitable clone (M54), the transcription template was produced by linearization of the plasmid DNA with SrfI. The plasmid M54 was deposited on September 30, 1997, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. 209312. The sequence comprising the coding region of rat GALR3 was subcloned into pBS KS$^+$AMV-pA50 (Nowak, et al., 1995) to produce M67. The transcription template was produced by linearization of the plasmid DNA with SrfI. The plasmid M67 was deposited on March 27, 1998, with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Designation No. 209708. mRNAs were transcribed using the T7 polymerase ("Message Machine", Ambion). Each oocyte received 2 ng each of GIRK1 and GIRK4 mRNA in combination with 25 ng of GalR3 mRNA. In other experiments oocytes received injections of mRNAs encoding the human α1A

adrenergic receptor, rGalR1 or rGalR2 galanin receptors (Forray et al., 1994; Parker et al., 1995) with or without GIRKs 1 and 4. After injection of mRNAs, oocytes were incubated at 17° for 3-8 days.--

Please delete the paragraph on page 156, lines 12-23, and insert the following replacement paragraph:

--The human GALR3 gene contains two in-frame METs: the first (as one reads 5' to 3') will be referred to herein as the "upstream MET" and the second (i.e., closer to TM1) will be referred to herein as the "downstream MET." Both the upstream and downstream METs are shown in Figure 4 (SEQ ID NO: 4). Based on data currently available, it is believed that the downstream MET is likely to be the correct initiating methionine. It is theoretically possible that the upstream MET might be the initiating MET. It is to be understood that the present invention includes both the receptor beginning at the downstream MET and the receptor beginning at the upstream MET.--

Please delete the Sequence Listing on pages 171-194 and replace it with the Sequence Listing attached hereto as **Exhibit 2.**

In the Claims:

Please cancel claims 1-239 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in a future continuation or divisional application.

Please add new claims 240-242 as follows:

--240. (New) A method of treating an abnormality in a subject wherein the abnormality is alleviated by administering

to the subject an amount of a GALR3 selective antagonist effective to treat the abnormality, wherein the antagonist binds to the GALR3 receptor with an affinity greater than ten-fold higher than the affinity with which it binds to a GALR1 receptor.--

--241. (New) The method of claim 240, wherein the abnormality is pain.--

--242. (New) The method of claim 240, wherein the abnormality is anxiety.--

Applicants submit herewith a marked-up copy of the amendments attached hereto as **Exhibit 1**.

REMARKS

Claims 1-239 were pending in the subject application. By this Preliminary Amendment, applicants have canceled claims 1-239 without prejudice or disclaimer and added new claims 240-242. Accordingly, upon entry of this Preliminary Amendment, claim 240-242 will be pending and under examination.

By this Preliminary Amendment, applicants have amended the specification to recite the continuing data for the above-identified application. Applicants have also amended the Title to more accurately describe the instant invention. Support for the amendment to the Title may be found *inter alia* in the specification, as originally-filed, on page 73, lines 11-15; and page 73, lines 27-28.

Applicants have further amended the specification to include the ATCC Deposit No. for plasmid M67. Applicants attach hereto as

Exhibit 4, a copy of the ATCC deposit receipt for plasmid M67. Applicants have also amended the specification to make uniform the recitation of "SEQ ID NO:." Applicants maintain that the additions to the specification raises no issue of new matter.

Applicants further maintain that the addition of new claim 240-242 raises no issue of new matter. Support for new claim 240 may be found *inter alia* in the specification, as originally-filed, on page 73, lines 11-15; page 73, lines 27-28; and page 74, lines 12-15. Support for new claim 241 may be found *inter alia* in the specification, as originally-filed, on page 73, lines 15-16. Support for new claim 242 may be found *inter alia* in the specification, as originally-filed, on page 73, line 15; and page 73, line 26. Accordingly, applicants respectfully request that this amendment be entered.

Sequence Listing:

The Sequence Listing in the subject application is identical to that of the parent of the subject application, U.S. Serial No. 09/058,333, filed on August 3, 1998. Applicants attach hereto as **Exhibit 2** and **Exhibit 3**, respectively, copies of the Sequence Listing (171-194 pages) and of the Statement In Accordance With 37 C.F.R. §1.821(f) (1 page), which were filed in connection with U.S. Serial No. 09/058,333 on August 3, 1998. The computer readable form in the subject application is identical to that filed in U.S. Serial No. 09/058,333 on August 3, 1998. In Accordance with 37 C.F.R. §1.821(e), please use the computer readable form filed in U.S. Serial No. 09/058,333 on August 3, 1998, as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the sequence listing that will be used for the instant

application.

Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following references which are on the attached Form PTO-1449 (**Exhibit 5**) were previously cited in connection with the prosecution of U.S. Serial No. 09/058,333 and PCT International Application NO. PCT/US97/18222 from which the subject application claims priority under 35 U.S.C. §120. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Office in connection with such prior applications need not accompany the Information Disclosure Statement. Accordingly, copies of the following references are not attached to this Information Disclosure Statement:

1. U.S. Patent No. 5,290,808, issued March 1, 1994, Sofia, et al.;

2. U.S. Patent No. 5,436,128, issued July 25, 1995, Harpold, et al.;

3. U.S. Patent No. 5,436,155, issued July 25, 1995, Bell, et al.;

4. U.S. Patent No. 5,462,856, issued October 31, 1995, Lerner, et al.;

5. U.S. Patent No. 5,508,164, issued April 16, 1996, Kausch, et al.

6. U.S. Patent No. 5,567,714, issued October 22, 1996, Bruns, et al.;

7. U.S. Patent No. 5,576,296, issued November 19, 1996, Bartfai, et al.;

8. PCT International Publication No. WO 92/15681, published September 17, 1992, Garvan Institute of Medical Research;

9. PCT International Publication No. WO 98/03548, International Publication Date 29 January 1998;

10. PCT International Publication No. WO 98/03059, International Publication Date 29 January 1998;

11. PCT International Publication No. WO 92/12997, published August 6,1992, The General Hospital Corporation;

12. PCT International Publication No. WO 92/15015, published September 3, 1992, Zymogenetic, Inc.;

13. PCT International Publication No. WO 95/22608 A1, published August 24, 1995, Amiranoff, et al.;

14. PCT International Publication No. WO 97/46681, published December 11, 1997, Bayer Corp.;

15. PCT International Publication No. WO 99/31130, published June 24, 1999;

16. European Patent Application No. 514 361 A1, published November 19, 1992, Aktiebolaget Astra;

17. European Patent Application No. 711 830 A2, published May 15, 1996, Takeda Chemical Industries, Ltd.;

18. Ahmad, A., et al., Identification And Molecular Cloning Of A Novel Galanin Receptor (GALR-2) In Rat Sensory Neurons", *Soc. Neurosci. Abstr.* (1996) 22(3): 1682, Abstract No. 661.10;

19. Ahmad, S., et al., "Molecular Cloning Of A Novel Widely Distributed Galanin Receptor Subtype (GALR2)," *International Association for the Study of Pain (IASP Press)(1996)* Abstract No. 81: 134;

20. Ahmad, S. Et al., Astra Pain Control (1996), poster;

21. Bartfai, T., et al, "Galanin Receptor Ligand M40 Peptide Distinguishes Between Putative Galanin-Receptor Subtypes," *PNAS* (USA)(1993) 90: 11287-11291;

22. Bouvier, M., et al., "Dynamic Palmitoylation of G-Protein-Coupled Receptors in Eukaryotic Cells," *Methods in Enzymology* (1995) 250: 300-314;

23. Bowie, et al., Deciphering the message in protein sequences: tolerance to amino acid substitutions. *Science* (1990) 247: 1306-1310;

24. Burgevin, M.C., et al., "Cloning, Pharmacological Characterization, and Anatomical Distribution of a Rat cDNA Encoding for a Galanin Receptor," *J. Molec. Neurosci.* (1995) 6: 33-41;

25. Chen, Y., et al., "Purification of a Galanin Receptor From Pig Brain," *PNAS* (USA) (1993) 90: 3845-3849;

26. Deecher, D.C., et al., "Galanin Receptors in Human Basal

Forebrain Differ From Receptors in the Hypothalamus: Characterization Using [^{125}I]Galanin (Porcine) and [^{125}I]Galantide," *J. Pharmocol. Exp. Ther.* (1995) 275: 720-727;

27. Gu, Z.F., et al., "Interaction of Galanin Fragments With Galanin Receptors on Isolated Smooth Muscle Cells From Guinea Pig Stomach: Identification of a Novel Galanin Receptor Subtype," *J.Pharmacol. Exp. Ther.* (1995) 272: 371-378;

28. Gustafson, E., et al., "Distribution of a Rat Galanin Receptor mRNA in Rat Brain," *Neuroreport* (1996) 7: 953-957;

29. Habert-Ortoli, E., et al., "Molecular Cloning of a Functional Human Galanin Receptor," *PNAS* (USA) (1994) 91: 9780-9783;

30. Heuillet, E., et al., "The Human Galanin Receptor: Ligand Binding and Functional Characteristics in the Bowes Human Melanoma Cell Line," *Eur. J. Pharmacol.* (1994) 269: 139-147;

31. Kahl, U., et al., "Galanin Receptors," *DN&P* (1995) 8(7): 404- 410;

32. Kask, K., et al., "Delineation of the Peptide Binding Site of the Human Galanin Receptor," *EMBO Journal* (1996) 15(2): 236- 244;

33. Lorimer, D., et al., "Cloning and Quantification of Galanin-1 Receptor Expression by Mucosal Cells Lining the Human Gastrointestinal Tract," *Biochem. Biophys. Res. Comm.* (1996) 222: 379-385;

34. Lorinet, A.M., et al., "Galanin Receptors in Human Hypothalamus: Biochemical and Structural Analysis," *Eur. J. Pharmacol.* (1994) 269: 59-64;

35. Marieb, E.N., (1992), *Human Anatomy And Physiology*, 2nd Edition, Redwood City, California, pp. 547-551;

36. O'Donnell, D., et al., "Neuroanatomical Distribution Of A Novel Rat Galanin Receptor Subtype," *Soc. Neurosci. Abstr.* (1996) 22(2): 1304, Abstract No. 517.9;

37. Parker, et al., "Cloning and Characterization of the Rat GALR1 Galanin Receptor From Rin14B Insulinoma Cells," *Molecular Brain Research* (1995) 34:(2), 179-189;

38. Reerk, et al., "'Homology' In Proteins And Nucleic Acids: A Terminology Muddle And A Way Out Of It," *Cell* (1987) 50: 667;

39. Selve et al., "Galanin receptor antagonists attenuate spinal antinociceptive effects of DAMGO, tramadol and non-opioid drugs in rats," *Brain Res.* (Oct. 7, 1996) **735(2)**: 177-187;

40. Valkna, A., et al., "Differential Regulation of Adenylate Cyclase Activity in Rat Ventral and Dorsal Hippocampus by Rat Galanin," *Neurosci. Lett.* (1995) 187: 75-78;

41. Wallace, et al., "Oligonucleotide probes for the screening of recombinant DNA libraries," Methods In Enzymology, Guide to Molecular Cloning Techniques, Berger et al. Eds, Academic Press (1987) 152: 432-442;

42. Walli, R., et al., "Identification and Biochemical

Characterization of the Human Brain Galanin Receptor," *J. Mol. Endocrinol.* (1994) 13: 347-356;

43. Wang et al., "Molecular cloning and pharmacological characterization of a new galanin receptor subtype" *Mol. Pharm.* **52**: 337-343 (Sept., 1997);

44. Wang et al., "Cloning and expressional characterization of a novel galanin receptor" *J. Biol. Chem.* **272(51)**: 31949-31952 (Dec. 19, 1997);

45. Watson, et al., *The G-Protein Linked Receptor Factbook,* Academic Press Limited (1994), San Diego, CA, pp. 2-6;

46. Wynick, D., et al., "Characterization of a High-Affinity Galanin Receptor in the Rat Anterior Pituitary: Absence of Biological Effect and Reduced Membrane Binding of the Antagonist M15 Differentiate it From the Brain/Gut Receptor," *PNAS* (USA) (1993) 90: 4231-4235;

47. Xu, X.J., et al., " New High Affinity Peptide Antagonists to the Spinal Galanin Receptor," *Br. J. Pharmacol.* (1995) 116: 2076-2080;

48. Xu et al., "Expression of galanin and a galanin receptor in several sensory systems and bone anlage of rat embryos," *Proc. Natl. Acad. Sci.* (Dec. 1996) **93**: 14901-14905;

49. Howard, A.D., et al., "Molecular cloning and characterization of a new receptor for galanin", Genbank Accession #RNU94322, published April 30, 1997;

50. Fathi, Z., et al., "Cloning, pharmacological characterization and distribution of a novel galanin receptor", Genbank Accession #AFO08548, published July 8, 1997;

51. Smith, K.E., et al., "Expression cloning of a rat hypothalamic galanin receptor coupled to phosphoinositide turnover", Genbank Accession #AFO10318, published September 30, 1997;

52. Wang, S., et al., "Cloning and expressional characterization of a novel galanin receptor. Identification of different pharmacophores within galanin for the three galanin receptor subtypes", Genbank Accession #AFO31522, published July 14, 1998; and

53. Connor, R., Genbank Accession #Z82241, published January 13, 1997.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone the number provided below.

No fee, other than the enclosed $370.00 fee for filing the subject application, is deemed necessary in connection with the filing of this Preliminary Amendment and Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDMENTS

Additions to the text are indicated by double underlining; deletions are indicated by square brackets.

In the Specification:

The replacement title on page 1, lines 4-5, and on page 236, line 1:

--[**DNA ENCODING GALANIN GALR3 RECEPTORS AND USES THEREOF**] **METHOD OF TREATING AN ABNORMALITY USING A GALR3 RECEPTOR ANTAGONIST**--

The replacement paragraph on page 1, after the title:

-- This application is a continuation of U.S. Serial No. 09/058,333, filed April 9, 1998, now allowed, which is a continuation-in-part of PCT International Application No. PCT/US97/18222, filed October 9, 1997, which is a continuation-in-part [in the U.S.] and claims priority of U.S. Serial No. 08/900,230, filed July 23, 1997, now allowed, which is a continuation-in-part of U.S. Serial No. 08/787,261, filed January 24, 1997, now abandoned, [which is a continuation-in-part of U.S. Serial No. 08/767,964, filed December 17, 1996, which is a continuation-in-part of U.S. Serial No. 08/728,139, filed October 9, 1996,] the contents of which are incorporated by reference. Throughout this application, various references are referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citation for these references may be found at the end of this application, preceding the sequence listing

and the claims. --

The replacement paragraph on page 8, line 33 through page 9, line 9:

--This invention provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within one of the two strands of the nucleic acid encoding the GALR3 receptor contained in plasmid K1086. This invention still further provides a nucleic acid probe comprising 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence described in Figure 1 ([Seq. ID No. 1] SEQ ID NO: 1) or (b) the reverse compliment to the nucleic acid sequence shown in Figure 1 ([Seq. ID No. 1] SEQ ID NO: 1).--

The replacement paragraph on page 9, lines 11-33:

--In yet another embodiment, the GALR3 receptor is the rat GALR3 receptor having substantially the same amino acid sequence as the amino acid sequence shown in Figure 2. In another embodiment, the GALR3 receptor is the rat GALR3 receptor having the amino acid sequence shown in Figure 2. In another embodiment, the GALR3 receptor is the human GALR3 receptor. In another embodiment, the GALR3 receptor is the human GALR3 receptor encoded by the coding sequence of plasmid pEXJ-hGalR3. This invention also provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique

sequence corresponding to a sequence present within one of the two strands of the nucleic acid encoding the GALR3 receptor contained in plasmid pEXJ-hGalR3. This invention provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence described in Figure 3 ([Seq. ID No. 3] SEQ ID NO: 3) or (b) the reverse compliment to the nucleic acid sequence shown in Figure 3 ([Seq. ID No. 3] SEQ ID NO: 3).--

The replacement paragraph on page 24, lines 3-6:

--**Figure 1** Nucleotide coding sequence of the rat hypothalamic galanin GALR3 receptor ([Seq. I.D. No. 1] SEQ ID NO: 1), with partial 5' and 3' untranslated sequences. Start and stop codons are underlined.--

The replacement paragraph on page 24, lines 7-10:

--**Figure 2** Deduced amino acid sequence of the rat hypothalamic galanin GALR3 receptor ([Seq. I.D. No. 2] SEQ ID NO: 2) encoded by the rat nucleotide sequence shown in Figure 1.--

The replacement paragraph on page 24, lines 12-15:

--**Figure 3** Nucleotide coding sequence of the human galanin GALR3 receptor ([Seq. I.D. No. 3] SEQ ID NO: 3), with partial 5' and 3' untranslated sequences. Start and stop codons are underlined.--

The replacement paragraph on page 24, lines 17-22:

--**Figure 4** Deduced amino acid sequence of the human galanin GALR3 receptor ([Seq. I.D. No. 4] SEQ ID NO: 4) encoded by the human nucleotide sequence shown in Figure 3.--

The replacement paragraph on page 24, lines 24-29:

--**Figures 5A-5D** Amino acid sequence alignment of the rat GALR3 receptor (top row) ([Seq. ID No. 2] SEQ ID NO: 2), human GALR3 receptor (middle row) ([Seq. ID No. 4] SEQ ID NO: 4) and rat GALR1 receptor (bottom row) ([Seq. ID No. 5] SEQ ID NO: 5). Transmembrane domains (TM 1-7) are indicated by brackets above the sequence.--

The replacement paragraph on page 29, line 13 through page 30, line 3:

---This invention provides an isolated nucleic acid encoding a GALR3 receptor having the same or substantially the same amino acid sequence as the amino acid sequence encoded by the plasmid K1086 (ATCC Accession No. 97747). In an embodiment, the nucleic acid is DNA. This invention further provides an isolated nucleic acid encoding a rat GALR3 receptor having the amino acid sequence encoded by the plasmid K1086. This invention provides an isolated nucleic acid encoding a GALR3 receptor having the same or substantially the same amino acid sequence as the amino acid sequence encoded by the plasmid pEXJ-RGalR3T (ATCC Accession No. 97826). In an embodiment, the nucleic acid is DNA. This invention further provides an isolated nucleic acid encoding a rat GALR3 receptor having the amino acid sequence encoded by the plasmid pEXJ-RGalR3T (ATCC Accession No. 97826). This invention provides an isolated nucleic acid encoding a GALR3 receptor having substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. I.D. No. 2] SEQ ID NO: 2). In

another embodiment, the GALR3 receptor is the rat GALR3 receptor having the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the nucleic acid comprises at least an intron. In still another embodiment, the nucleic acid comprises alternately spliced nucleic acid transcribed from the nucleic acid contained in plasmid K1086. In an embodiment, the alternately spliced nucleic acid is mRNA transcribed from DNA encoding a galanin receptor.--

The replacement paragraph on page 30, lines 5-18:

---In an embodiment, the GALR3 receptor is a human GALR3 receptor. This invention provides an isolated nucleic acid encoding a human GALR3 receptor having the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). This invention provides an isolated nucleic acid encoding a human GALR3 receptor, wherein the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 34, line 33 through page 35, line 10:

--This invention also provides an isolated galanin GALR3 receptor protein. In one embodiment, the GALR3 receptor protein has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid

K1086. In another embodiment, the GALR3 receptor protein has the amino acid sequence encoded by plasmid K1086. In another embodiment, the protein has the amino acid sequence encoded by the plasmid pEXJ-hGalR3. In an embodiment, the GALR3 receptor protein has the same or substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. I.D. No. 2] SEQ ID NO: 2). In an embodiment, the GALR3 receptor comprises the same or substantially the same amino acid sequence as the amino acid sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 38, lines 29-30:

--This invention provides a plasmid designated M67 (ATCC [Accession] Designation No. 209708).--

The replacement paragraph on page 38, line 32 through page 39, line 1:

--This plasmid (M67) was deposited on March 27, 1998, with the American Type Culture Collection (ATCC), [12301 Parklawn Drive, Rockville, Maryland 20852,] 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC [Accession] Designation No. [xxxxx] 209708.--

The replacement paragraph on page 40, line 35 through page 41, line 5:

---This invention still further provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence

corresponding to a sequence present within (a) the nucleic acid sequence shown in Figure 1 ([Seq. ID No. 1] SEQ ID NO: 1) or (b) the reverse complement to the nucleic acid sequence shown in Figure 1 ([Seq. ID No. 1] SEQ ID NO: 1).--

The replacement paragraph on page 41, lines 7-20:

--This invention also provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within one of the two strands of the nucleic acid encoding the GALR3 receptor contained in plasmid pEXJ-hGalR3. This invention provides a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with a nucleic acid encoding a GALR3 receptor, wherein the probe has a unique sequence corresponding to a sequence present within (a) the nucleic acid sequence shown in Figure 3 ([Seq. ID No. 3] SEQ ID NO: 3) or (b) the reverse complement to the nucleic acid sequence shown in Figure 3 ([Seq. ID No. 3] SEQ ID NO: 3).--

The replacement paragraph on page 48, line 16 through 49, line 15:

--In one embodiment, the GALR3 receptor is a mammalian GALR3 receptor. In another embodiment, the GALR3 receptor is a rat GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid K1086. In still another embodiment, the GALR3 receptor has the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid

sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In still another embodiment, the cells are transfected with the plasmid pEXJ-RGALR3T (ATCC Accession No. 97826), encoding the rat GALR3 receptor. Plasmid pEXJ-RGalR3T comprises the entire coding region of rat GALR3, but in which the 5' initiating ATG is joined directly to the vector, and which comprises only 100 nucleotides from the 3' untranslated region after the stop codon (i.e., up to and including nucleotide 1275 in Figure 1 ([Seq. ID NO. 1] SEQ ID NO: 1)). Transfection of cells with the "trimmed" plasmid results in a higher level of expression of the rat GALR3 receptor than the level of expression when plasmid K1086 is used. The use of the "trimmed" plasmid provides for greater convenience and accuracy in binding assays. In another embodiment the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In an embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 50, line 17 through 51, line 4:

---In one embodiment, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has

the same or substantially the same amino acid sequence as that encoded by the plasmid K1086. In yet another embodiment, the GALR3 receptor has the amino acid sequence encoded by the plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment of this invention the cells are transfected with plasmid pEXJ-RGalR3T (ATCC Accession No. 97826).--

The replacement paragraph on page 51, line 29 through 52, line 15:

---In an embodiment, the GALR3 receptor is a mammalian GALR3 receptor. In one embodiment of the invention, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by the plasmid K1086. In still another embodiment, the GALR3 receptor has the amino acid sequence encoded by the plasmid K1086. In another embodiment, the GALR3 receptor

has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3_receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 53, lines 17-19:

--In an embodiment of any of the above processes, the cells are injected with RNA synthesized in vitro from the plasmid designated M67 (ATCC [Accession] Designation No. 209708).--

The replacement paragraph on page 58, line 34 through 59, line 21:

---In an embodiment of any of the above processes, the GALR3 receptor is a mammalian GALR3 receptor. In another embodiment of the above processes, the GALR3 receptor is a rat GALR3 receptor or a human GALR3 receptor. In still another embodiment of the above processes, the GALR3 receptor has the same or substantially the same amino acid sequence as encoded by the plasmid K1086 (ATCC Accession

No. 97747). In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment of this invention the cells are transfected with plasmid pEXJ-RGalR3T (ATCC Accession No. 97826).--

The replacement paragraph on page 61, line 20 through 62, line 5:

---In an embodiment of any of the above processes, the GALR3 receptor is a mammalian GALR3 receptor. In an embodiment of the above-described methods, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the

GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 63, lines 5-26:

---In an embodiment of any of the above-described methods, the GALR3 receptor is a rat GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In another embodiment, the GALR3 receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3

receptor has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 64, line 33 through page 65, line 26:

--In an embodiment of any of the above-described methods, the GALR3 receptor is a rat GALR3 receptor. In another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as the amino acid sequence encoded by plasmid K1086. In another embodiment, the GALR3 receptor has substantially the same amino acid sequence as the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor has the amino acid sequence shown in Figure 2 ([Seq. ID No. 2] SEQ ID NO: 2). In another embodiment, the GALR3 receptor is a human GALR3 receptor. In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid pEXJ-RGalR3T (ATCC Accession No. 97826). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid M54 (ATCC Accession No. 209312). In still another embodiment, the GALR3 receptor has the same or substantially the same amino acid sequence as that encoded by plasmid M67 (ATCC [Accession] Designation No. 209708). In another embodiment, the human GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as the sequence shown in Figure 4 ([Seq. I.D. No. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In another embodiment, the GALR3 receptor

has a sequence, which sequence comprises the sequence shown in Figure 4 ([Seq. ID NO. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 68, line 32 through page 69, line
15:

--In an embodiment of any of the above-described processes, the GALR3 receptor is a mammalian GALR3 receptor. In another embodiment of any of the above-described processes, the GALR3 receptor has substantially the same amino acid as encoded by the plasmid K1086 (ATCC Accession No. 97747). In another embodiment of any of the above-described processes, the GALR3 receptor has substantially the same amino acid sequence as that shown in Figure 2 ([Seq. ID NO. 2] SEQ ID NO: 2}. In still another embodiment of any of the above-described processes, the GALR3 receptor has substantially the same amino acid sequence as encoded by the plasmid pEXJ-hGalR3 (ATCC Accession No. 97827). In an embodiment of any of the above-described processes, the GALR3 receptor has a sequence, which sequence comprises substantially the same amino acid sequence as that shown in Figure 4 ([Seq. ID NO. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427. In still another embodiment of any of the above-described processes, the GALR3 receptor has a sequence, which sequence comprises a sequence shown in Figure 4 ([Seq. ID NO. 4] SEQ ID NO: 4) from amino acid 60 through amino acid 427.--

The replacement paragraph on page 98, lines 7-18:

--Human brain multiple tissue northern blots (MTN brain blots II and III, Clontech, Palo Alto, CA) and human peripheral MTN blot (Clontech, Palo Alto, CA) carrying mRNA

(2 µg) purified from various human brain areas and peripheral tissues, respectively, were hybridized at high stringency with overlapping probes directed to the amino-terminus of hGALR3
5' GATGGCTGATGCCCAGAACATTTCACTGGACAGCCCAGGGAGTGT 3'
([SEQ ID NO. 51] SEQ ID NO: 51) and
5' GACCACAGGCACTGCCACGGCCCCCACACTCCCTGGGCTGTCCAG 3'
([SEQ ID NO. 52] SEQ ID NO: 52),according to the manufacturer's specifications.--

The replacement paragraph on page 98, lines 21-34:

--Tissues were homogenized and total RNA extracted using the guanidine isothiocyanate/CsCl cushion method. RNA was then treated with DNase to remove any contaminating genomic DNA and poly A^+-selected using FastTrack kit (Invitrogen), according to manufacturer's specifications. cDNA was prepared from mRNA with random hexanucleotide primers using reverse transcriptase Superscript II (BRL, Gaithersburg, MD). First strand cDNA (corresponding to ≈5 ng of poly A^+ RNA) was amplified in a 50 µL PCR reaction mixture with 300 nM of forward (directed to the amino-terminus: ([SEQ ID NO. 24] SEQ ID NO: 24) and reverse (directed to the third intracellular loop: ([SEQ ID NO. 27] SEQ ID NO: 27)) primers, using the thermal cycling program and conditions described above.--

The replacement paragraph on page 98, line 37 through page 99, line 13:

--The PCR products were run on a 1.5% agarose gel and transferred to charged nylon membranes (Zetaprobe GT, BioRad), and analyzed as Southern blots. GALR3 primers were screened for the absence of cross-reactivity with the other galanin receptors. Filters were hybridized with a

radiolabeled probe directed to the first intracellular loop,
5'-TGCAGCCTGGCCCAAGTGCCTGGCAGGAGCCAAGCAGTACCACAG-3' ([Seq. I.D. No. 53] SEQ ID NO: 53), and washed under high stringency. Labeled PCR products were visualized on X-ray film. Similar PCR and Southern blot analyses were conducted with primers and probes directed to the housekeeping gene, glyceraldehyde phosphate dehydrogenase (G3PDH; Clontech, Palo Alto, CA), to normalize the amount of cDNA used from the different tissues.--

The replacement paragraph on page 99, lines 15-27:

--RT-PCR was performed on human pituitary cDNA (two sources: Clontech cDNA and cDNA prepared from poly A+RNA purchased from ABS) using the following conditions: 94°C for 30 sec and 68°C for 2 min, for 40 cycles, with a preincubation at 94°C for 2 min and a postincubation at 68°C for 5 minutes. Primers specific for human GALR1 were used (KS1177; [SEQ ID NO. 35] SEQ ID NO: 35 and KS1178; [SEQ ID NO. 36] SEQ ID NO: 36). Primers specific for human GALR2 were used (BB183; [SEQ ID NO. 60] SEQ ID NO: 60 and BB184; [SEQ ID NO. 61] SEQ ID NO: 61). Primers specific for human GALR3 were used (BB444; [SEQ ID NO. 62] SEQ ID NO: 62 and BB445; [SEQ ID NO. 63] SEQ ID NO: 63). Primers specific for human prolactin were used (BB446; [SEQ ID NO. 64] SEQ ID NO: 64 and BB447; [SEQ ID NO. 65] SEQ ID NO: 65).--

The replacement paragraph on page 99, line 31 through page 100, line 8:

--BB183: 5'-TCAGCGGCACCATGAACGTCTCGGGCT-3' ([SEQ ID NO. 60] SEQ ID NO: 60).

BB184: 5'-GGCCACATCAACCGTCAGGATGCT-3' ([SEQ ID NO. 61]

SEQ ID NO: 61)

BB444: 5'-ATGGCTGATGCCCAGAACATTTCAC-3' ([SEQ ID NO. 62] SEQ ID NO: 62).

BB445: 5'-TAGCGCACGGTGCCGTAGTAGCTGAGGT-3' ([SEQ ID NO. 63] SEQ ID NO: 63).

BB446: 5'-ATGAAAGGGTCCCTCCTGCTGCTGCT-3' ([SEQ ID NO. 64] SEQ ID NO: 64).

BB447: 5'-TATCAGCTCCATGCCCTCTAGAAGCC-3' ([SEQ ID NO. 65] SEQ ID NO: 65).--

The replacement paragraph on page 110, line 22 through page 112, line 10:

--Oocytes were isolated as described above, except that 3 mg/mL collagenase was used to defolliculate the oocytes. Genes encoding G-protein inwardly rectifying K^+ channels 1 and 4 (GIRK1 and GIRK4) were obtained by PCR using the published sequences (Kubo et al., 1993; Dascal et al., 1993; Krapivinsky et al., 1995b) to derive appropriate 5' and 3' primers. Human heart cDNA was used as template together with the primers
5'-CGCGGATCCATTATGTCTGCACTCCGAAGGAAATTTG-3' (SEQ ID NO[.]: 54) and
5'-CGCGAATTCTTATGTGAAGCGATCAGAGTTCATTTTTC -3' (SEQ ID NO[.]: 55) for GIRK1 and
5'-GCGGGATCCGCTATGGCTGGTGATTCTAGGAATG-3' (SEQ ID NO[.]: 56) and
5'- CCGGAATTCCCCTCACACCGAGCCCCTGG-3' (SEQ ID NO[.]: 57) for GIRK4. In each primer pair, the upstream primer contained a BamHI site and the downstream primer contained an EcoRI site to facilitate cloning of the PCR product into pcDNA1-Amp (Invitrogen). The transcription template for hGalR3 was obtained similarly by PCR using the cloned cDNA in

combination with primers
5'-CCAAGCTTCTAATACGACTCACTATAGGGCCACCATGGCTGATGCCCAGA-3' (SEQ ID NO[.]: 58) and
5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGCAGGG TTTATTCCGGTCCTCG-3' (SEQ ID NO[.]: 59). Alternatively, the complete coding region of hGalR3 is subcloned into the high-efficiency transcription vector pBS KS$^+$ AMV-pA50 (Nowak et al., 1995). This plasmid was modified by adding the recognition sequence for the restriction enzyme SrfI downstream of the poly A sequence in the plasmid. The new plasmid was designated M52. Subcloning involved the isolation of a 1.1 kb NcoI/EcoRI restriction fragment encoding the entire hGALR3 gene followed by its ligation into NcoI/EcoRI digested M52. After identification of a suitable clone (M54), the transcription template was produced by linearization of the plasmid DNA with SrfI. The plasmid M54 was deposited on September 30, 1997, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. 209312. The sequence comprising the coding region of rat GALR3 was subcloned into pBS KS$^+$AMV-pA50 (Nowak, et al., 1995) to produce M67. The transcription template was produced by linearization of the plasmid DNA with SrfI. The plasmid M67 was deposited on March 27, 1998, with the American Type Culture Collection (ATCC), [12301 Parklawn Drive, Rockville, Maryland 20852,] 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC [Accession] Designation No. [xxxxxx] 209708. mRNAs were transcribed using the T7 polymerase ("Message Machine", Ambion). Each oocyte received 2 ng each of GIRK1 and GIRK4

mRNA in combination with 25 ng of GalR3 mRNA. In other experiments oocytes received injections of mRNAs encoding the human α1A adrenergic receptor, rGalR1 or rGalR2 galanin receptors (Forray et al., 1994; Parker et al., 1995) with or without GIRKs 1 and 4. After injection of mRNAs, oocytes were incubated at 17° for 3-8 days.--

The replacement paragraph on page 156, lines 12-23:

--The human GALR3 gene contains two in-frame METs: the first (as one reads 5' to 3') will be referred to herein as the "upstream MET" and the second (i.e., closer to TM1) will be referred to herein as the "downstream MET." Both the upstream and downstream METs are shown in Figure 4 ([Seq. ID No. 4] SEQ ID NO: 4). Based on data currently available, it is believed that the downstream MET is likely to be the correct initiating methionine. It is theoretically possible that the upstream MET might be the initiating MET. It is to be understood that the present invention includes both the receptor beginning at the downstream MET and the receptor beginning at the upstream MET.--